REMARKS/ARGUMENTS

Claims 1-4, 7-20, 78, and 79 are pending. Claims 1, 8, 12, 19, 78, and 79 are amended. New claims 93-100 are added. Claims 5, 6, 21-77, and 80-92 are cancelled. No new matter has been added.

Restriction Requirement

Applicant cancels claims 21-77 and 80-89, drawn to a non-elected invention, and reserve the right to pursue the non-elected invention in a divisional application.

Claim Rejection – 35 U.S.C. §112, 2d paragraph

Applicant respectfully submits that claims 8 and 19 are proper as filed in view of M.P.E.P. §2173.05(h), part II. However, in order to further prosecution, Applicant has amended claims 8 and 19 to recite traditional markush language.

Claim Rejection – 35 U.S.C. §102(b)

In the Office action claims 1, 2, 4, 7, 8, 10-13, 15-19, and 78-79 have been rejected under 35 U.S.C. §102(b) as allegedly being unpatentable over U.S. patent No. 5,225,204 to Chen et al. ("the Chen patent"). This rejection is respectfully traversed as the Chen patent does not teach every element of the claimed invention.

The Chen patent does not teach drug dosage forms prepared by compacting thyroid hormone and at least one pharmaceutically acceptable excipient under compression pressures of less then 5000 psi/g as recited in claims 1, 2, 4, 7, 8, 10, 11, 17-19, 78, 79. Preparing dosage forms at compression pressures less than 5000 psi/g reduces undesirable moisture

induced degradation of a thyroid hormone thereby producing more stable dosage forms. Not only does the Chen patent fail to teach any specific compaction pressure, the Chen patent's formulations are not stable. See Declaration of Dr. Spiridon Spireas attached hereto.

U.S. Patent No 5,955,105 to Mitra, a reference contemporaneous to the Chen patent, reports that the compositions taught by the Chen patent are *not* stable. See Col 2, lines 5-58. Indeed, the Chen patent does not quantify the stability of the described compounds or describe how preparation techniques affect stability characteristics.

Conventional compaction techniques, as are described in the Chen patent, release equilibrium moisture from excipient particles which are in close contact with the co-compressed drug particles. This liberated equilibrium moisture in turn reacts with, and thereby degrades, the thyroid hormone.

In contrast to the teachings of the Chen patent, Applicant has discovered that degradation of the thyroid hormone is reduced when dosage forms are prepared using compression pressures of less than 5000 psi/g because these compression pressures limit the amount of residual moisture liberated from excipient particles during compaction.

With respect to claims 12-13 and 15-19 as amended, the Chen patent does not teach dosage forms including a thyroid hormone that is treated with a hydrophobic solid powder to substantially "water-proof" the thyroid hormone. Although, the Chen patent teaches that magnesium stearate, a hydrophobic powder, is a suitable lubricant, nowhere does Chen teach the treatment of thyroid hormone with magnesium stearate to prevent moisture induced degradation. In fact, the Chen patent teaches the addition of magnesium stearate only after the purported stabilization of levothyroxine according to Chen's techniques. See Col.6, 14-

52. Thus, the Chen patent fails to teach dosage forms wherein thyroid hormone is *treated* with a hydrophobic solid powder.

In contrast, Applicant has discovered that treating thyroid hormone with a hydrophobic solid powder substantially water-proofs the thyroid hormone thereby reducing the incidence of moisture induced degradation. As shown in Table 5, unit dosage forms including thyroid hormone treated with a hydrophobic solid powder exhibited reduced degradation compared to commercially available levothyroxine. For example, 4 dosage forms including 0.025 mg levothyroxine sodium treated with 10.0 mg, 5.0 mg, 2.5 mg, and 1.0 mg exhibited 0.0, 5.9, 3.9, and 9.5 weight percent decrease in the weight of levothyroxine sodium, respectively, after being stored at 60°C and a relative humidity of 75% for 5 days. For comparison, 0.025 mg of commercially available levothyroxine sodium exhibited a 36.7 weight percent decrease in the weight of the thyroid hormone after being stored at the same conditions. See page 14.

Accordingly, since the Chen patent does not teach all of the elements of Applicant's claims 1, 2, 4, 7, 8, 10-13, 15-19, and 78-79, withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claim Rejection – 35 U.S.C. §103(a)

Claims 1-2, 4, 7-13, 15-20, and 78-79 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Chen patent. Claims 1-2, 4, 7-13, 15-20, and 78-79 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Chen patent in view of the Mitra patent. Claims 1-4, 7-20, and 78-79 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Chen patent in view of the Sakar

patent or the Yamamoto patent. Claims 1, 7-12, 16-20, and 78-79 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Mitra patent in view of the Schor patent or the Maish patent. Applicant traverses these rejections because combinations of the Chen, Mitra, Sarkar, Schor, and Yamamoto patents would not have produced any claimed invention, even if it were assumed for the sake of argument that such a combination is one that those of ordinary skill would have been motivated to make.

The Chen, Mitra, Sarkar, Schor, and Yamamoto patents do not teach or suggest drug dosage forms prepared by compacting thyroid hormone and at least one pharmaceutically acceptable excipient under compression pressures of less then 5000 psi/g as recited in claims 1-4, 7-11, 17, 18, 78, and 79. Without such a teaching, the present claims cannot be found to be obvious in view of the Chen, Mitra, Sarkar, Schor, and Yamamoto patents.

In contrast to the recited dosage forms, the Mitra Patent teaches levothyroxine formulations prepared using a conventional tableting machine using traditional techniques. Nowhere does the Mitra patent describe methods of preparing unit dosage forms with low compression techniques to improve stability characteristics as in the recited dosage forms. Applicant's dosage forms exhibit improved stability as shown in Table 5, described above.

Although the Schor patent teaches thyroid hormone compositions prepared using "compression pressures of 2000 to 16000 psi," (Col 5, lines 36-37) this teaching is meaningless compared to the pending claims because it uses units of measurement different from the pending claims to quantify compaction pressure. Comparing the compression pressure range of the Schor patent and the range recited by the Applicant is like comparing apples to oranges. In contrast to the Schor patent's use of compaction pressures in pound per square inch, i.e., compression *independent* of mass of the dosage form, Applicant recites

compaction pressures in pounds per square inch per gram, i.e., units *dependent* of the size of the unit dosage form being compressed.

Using the same system of measurement recited in the pending claims, the Schor patent teaches compression pressures that are significantly higher than those recited by Applicant. For example, Example 6 describes the preparation of a 717 mg tablet by compressing it at 5000 psi. A compression pressure of 5000 psi applied to a 717 mg tablet yields a compression pressure of roughly 6973.5 psi/gram (5000 / 0.717). Therefore, the Schor patent does not teach or suggest unit dosage forms prepared by using compression pressures less than 5000 psi/g.

The Maish patent does not teach dosage forms of thyroid hormone. It disclosed only compositions of acetaminophen. Therefore, the Maish patent does not teach thyroid formulations having the same stability characteristics as the pending claims.

The Sarkar and Yamamoto patents are used by the Office Action to teach capsule shells composed of hydroxypropyl methylcellulose. These patents clearly do not teach low pressure preparation techniques that improve the stability characteristics of unit dose forms.

Therefore, the Chen, Mitra, Sarkar, Schor, and Yamamoto patents do not teach unit dosage forms prepared by using compression pressures less than 5000 psi/g. There is simply no suggestion to utilize the same. Without such a suggestion, claims 1-4, 7-11, 17, 18, 78, and 79 cannot be found obvious over the Scott patent.

With respect to claims 12-13 and 15-19 as amended, the Chen, Mitra, Sarkar, Schor, and Yamamoto patents do not teach or suggest dosage forms including a thyroid hormone that is *treated* with a hydrophobic solid powder to substantially "water-proof" the thyroid hormone. The Office Action points to no legally sufficient motivation for its proposed

modification of the Chen, Mitra, Sarkar, Schor, and Yamamoto patents. Indeed, the cited references do not even recognize the incidence of moisture induced degradation caused by equilibrium moisture liberated during compaction.

Since the Chen, Mitra, Sarkar, Schor, and Yamamoto patents do not teach or suggest drug dosage forms the proposed combination of their respective teaching could not possibly have produced any claimed invention. Accordingly, the rejection for alleged obviousness is improper and should be withdrawn. To establish a prima facie case of obviousness, all limitations set forth in a patent claim must be taught or suggested in the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Applicant believes that the foregoing is a full and complete response to the Office Action of record.

Date: December 15, 2003

Stephen C. Timmins
Registration No. 48,481

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DECLARATION OF SPIRIDON SPIREAS

1. I, Dr. Spiridon Spireas, am the sole inventor of U.S. Patent Application Serial N . 09/690,973, filed October 18, 2000. I received a Bachelors of Science degree in pharmacy from National University of Greece in 1985. In 1993, I received a Doctor of Philosophy degree in pharmaceuticals and industrial pharmacy. After working for seven years as a professor, I started my employment with Mutual Pharmaceuticals Corporation ["Mutual"] in 1999. I am currently the Vice President of Research and Development with responsibility for all aspects of pharmaceutical development and laboratory operation at Mutual.

A. Levothyroxin Sodium Exhibits Poor Stability

2. I am aware thyroid hormone, such as for example levothyroxine sodium have a relatively brief shelf life due to their susceptibility to moisture induced degradation. Levothyroxine sodium is hygroscopic and degrades rapidly in the presence of high humidity, light, high temperature or in the presence of certain commonly used pharmaceutical excipients, such as carbohydrates, including lactose, sucrose, dextrose and starch. I understand that the pharmaceutical industry seeks stable formulations of thyroid hormone having a longer shelf life and methods for making the same.

B. Levothyroxin Sodium Formulations Described In U.S. Patent No. 5,225,204 to Chen et al. Exhibit Poor Stability.

3. I have analyzed U.S. Patent No. 5,225,204 to Chen *et al.* ("the Chen patent"). I understand that the Chen patent describes formulations of levothyroxine sodium mixed with a cellulose carrier (such as microcrystalline cellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, or hydroxypropylmethyl cellulose), in the presence of a cellulose complexing agent, a polar organic solvent, or both. Such

formulations are then pressed into tablets using a conventional tablet pressing machine. The Chen patent also describes formulations prepared by mixing levothyroxine sodium and polyvinylpyrrolidone (PVP) to produce a dry mixture which can then be dissolved in or mixed with a polar organic solvent to effect "molecular complexing of the levothyroxine sodium and ... the PVP."

4. The shelf life and stability of drug formulations described by the Chen patent can not be determined without additional bench testing because no stability data is reported. Thus, one would need to prepare and test the formulations described in the Chen patent in order to determine the formulation's stability and shelf life.

5. I am aware that a contemporaneous reference, U.S. Patent No. 5,955,105 to Mitra, *et al.* ("the Mitra patent"), examined the stability of compounds prepared according to the Chen patent. The compounds were found to have poor stability.

6. I have analyzed the Mitra patent. The Mitra patent describes tablets prepared according to the Chen patent and reports the results of a stability analysis performed on such tablets. Stability results are reported at ambient room temperature, at 30°C, and at 40°C with no humidity control. I understand that these procedures used to test the compounds prepared according to the Chen patent are conventional tests used by the pharmaceutical industry.

7. As reported by the Mitra patent, the stability results for formulations prepared according to the Chen patent clearly exhibit poor stability and hence a relatively short shelf life. As reported by the Mitra patent, the stability of formulations described in the Chen patent is substantially worse than already-available commercial products.

8. I am also aware that it is well known in the pharmaceutical industry that complexes of levothyroxine sodium and PVP as described in the Chen patent produce formulations that readily degrade when contacted with water. Such formulations are not stable.

C. The Chen Patent Does Not Teach Unit Dosage Forms Prepared by Compaction Techniques Using Compression Pressures Less Than 5000 psi/g

9. The Chen patent does not teach thyroid hormone formulations prepared using compression pressures below 5000 psi/g. The Chen patent teaches preparation of dosage forms with a conventional tablet press. There is no indication that compression pressures below 5000 psi/g are utilized to prepare dosage forms.

10. I understand that the pharmaceutical industry regularly compacts solid dosage forms at compression pressures greater than 5000 psi/g to produce tablets of acceptable hardness.

11. The Chen patent does not recognize the incidence of moisture induced degradation caused by equilibrium moisture liberated during compaction at high compression pressures.

12. A research chemist with about one year of work experience would not have been motivated to modify the compositions described in the Chen patent to achieve stable drug formulations of levothyroxine sodium. There is simply no motivation to do so given the results reported in the Mitra patent. Similarly, a research chemist with about one year of work experience would not have been motivated to achieve stable dosage formulations by compacting solid dosage forms at compression pressures less than 5000 psi/g.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: December 15, 2003

Spiros Spireas

Dr. Spiridon Spireas
Vice President of Research and Development
Mutual Pharmaceuticals Corporation